

## Homocysteine Levels, Haemostatic Risk Factors and Patency Rates After Endovascular Treatment of the Common Iliac Arteries

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**Objectives.** To investigate the impact of clinical risk factors, plasma homocysteine and haemostatic variables on the results after endovascular treatment of symptomatic atherosclerosis of the common iliac artery.

**Design.** Prospective observational study.

**Setting.** University hospital.

**Patients and method.** The study included 139 technically successful interventions in 103 patients. Technical success was defined as  $\leq 30\%$  residual stenosis as seen on the post treatment angiogram. Blood samples for analyses of fasting plasma values of homocysteine, fibrinogen, D-dimer, activated protein C resistance were drawn upon admission. Median follow-up for all procedures was 22 months (range 0–55 months). Patency was defined as freedom from  $\geq 50\%$  restenosis or reocclusion.

**Results.** The technical success rate for all procedures was 93%. The 1-year cumulative primary patency rate based on intention to treat was 85%. Multivariate analysis revealed a significant independent association between patency rates and levels of fibrinogen and homocysteine and the nature of the lesion treated (stenosis vs. occlusion).

**Conclusion.** The aetiology of restenoses and reocclusions is probably multifactorial. Procoagulant activity, the nature of the lesion treated and homocysteine levels within and above the upper range of normal limits are important risk factors for failure after endovascular treatment of the common iliac arteries.

**Keywords:** Restenosis; Reocclusion; Homocysteine; D-Dimer; Fibrinogen; PTA; Common iliac arteries; Survival analysis.

### Introduction

Patency rates after percutaneous transluminal angioplasty (PTA) for treatment of intermittent claudication caused by occlusive disease of the common iliac arteries are reported to be 65% after treatment of stenoses and 54% after treatment of occlusions at four years.<sup>1,2</sup> The 4-year patency rates of angioplasties for critical limb ischaemia are lower, 53% after treatment of stenoses and 44% for occlusions. Iliac stenting improves patency to 77 and 61% after treatment of stenoses and occlusions for intermittent claudication, 67 and 53% after treatment of stenoses and occlusions for critical limb ischaemia after four years.<sup>1</sup> Early failures are attributed to myointimal hyperplasia

triggered by the mechanical trauma of angioplasty.<sup>3</sup> Later failures are ascribed to the progress of the atherosclerotic disease.<sup>4</sup>

Failure after vascular and endovascular surgery is associated with a variety of factors: young age and gender,<sup>5,6</sup> the severity of ischaemia, the nature of the lesion treated and run-off.<sup>1,7,8</sup> Enhanced procoagulant and inflammatory markers such as elevated pre-treatment levels of fibrinogen, D-dimer and activated protein C resistance are associated with restenosis after angioplasty.<sup>9,10,11</sup> Elevated plasma homocysteine is an independent risk factor for atherosclerosis,<sup>12</sup> though not clearly linked to an increased risk of recurrence after cardiovascular intervention.<sup>13,14</sup> The results of the nine studies hitherto published on the association between failure after peripheral vascular surgery and homocysteine levels are ambiguous.<sup>9,15–22</sup> In our earlier studies, we

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found elevation of D-dimer levels predictive of failure after endovascular treatment of the above-knee femoro-popliteal artery,<sup>9</sup> and low values of homocysteine predictive of restenosis after carotid endarterectomy.<sup>19</sup>

Conditions of flow and shear stress are important for the development of intima hyperplasia<sup>23,24</sup> and risk of failure may vary depending on the anatomical localisation of the lesion in the vascular tree as well as the treatment modality studied. The different physiological properties of the artery (i.e. muscular or elastic) determine the response to the trauma of endovascular treatment.<sup>25</sup> The variation in the properties of the endothelial cells may contribute these differences.<sup>26</sup> To avoid confounders, it is of importance to examine the results of one treatment modality at a well defined anatomical site.

The aim of the present study is to investigate the relationship between plasma levels of homocysteine and other haemostatic and clinical risk factors and restenosis or reocclusion after endovascular treatment of symptomatic atherosclerosis of the common iliac arteries.

### Patients and Methods

From October 1999 to October 2003, a prospective study of 197 primary endovascular interventions of the common iliac arteries in 149 patients done at our institution was performed. Percutaneous transluminal angioplasty (PTA) was carried out in 96 cases and additional stenting in 101 cases.

Technical success was defined as a residual stenosis <30% on the post-treatment angiogram. In cases with a doubtful result, intraarterial pressure measurement proximally and distally to the lesion was used for clarification.<sup>27</sup> A post-treatment pressure gradient < 5 mmHg was accepted as a criterion for success.

Thirteen procedures (nine PTA's and four stents) were excluded from the study because of technical failure. Forty procedures were registered as lost to follow-up because of missing duplex-ultrasound examination or angiography to confirm the status of patency. Ten patients (13 procedures) died early (<6 months after the procedure) in the follow up period and 18 patients (27 procedures) had either moved too far away, could not be reached by telephone or post or refused to participate in the study. Five cases in which the study blood tests were not taken were likewise excluded. Thus the study included 139 successful procedures in 103 patients.

The study group consisted of 79 men (77%) and 24 women (33%) with a mean age of 62 years (range 41–88

**Table 1. Risk factors in 103 patients subjected to endovascular treatment of 139 common iliac artery stenoses or occlusions**

Risk factor	%
Heart disease	31
Hypertension, medically treated	30
Diabetes Mellitus	15
COPD	4
Stroke	11
Smoking	71
Se-creatinine > 125 µmol/l	6

COPD denotes chronic obstructive pulmonary disease.

years). Risk factors are listed in Table 1. The indication for treatment was intermittent claudication in 112 cases (81%) and critical ischaemia in 27 (19%). Critical ischaemia was defined according to the second European Consensus Document on chronic critical leg ischaemia.<sup>28</sup>

The quality of run-off was classified into two groups according to following criteria: group a: patent superficial femoral, profunda femoris and popliteal arteries without significant stenoses as well as cases with runoff into a patent femoro-femoral cross-over bypass, with or without patent ipsilateral and contralateral superficial femoral arteries. Group B: Occluded or stenotic (≥50%) superficial femoral and/or popliteal arteries. The external iliac artery was patent and without significant stenoses in all cases.

The mean length of all lesions was 2.2 cm (range 0.5–8 cm). The mean length of occlusions was 4.7 cm (range 0.5–8 cm). The endovascular technique applied was as described by Dotter and Judkins.<sup>29</sup> PTA with stenting was routinely applied for treatment of occlusions. PTA alone was the standard treatment of stenoses. However, selective stenting was performed if the result of PTA alone was deemed unsatisfactory due to residual stenosis, in cases complicated with dissection (5 cases) or perforation (1 case).

All cases treated with stent were given Heparin 5000 i.u. intravenously during the procedure. If tolerated, Aspirin 160 mg was prescribed on a daily basis thereafter. No other platelet-inhibiting medication was prescribed if Aspirin treatment was contraindicated (26 of 139 cases (27%)).

Follow up was routinely performed at 1 and 12 months with ankle-arm pressure measurement and clinical evaluation. Recurrent symptoms were considered to be a sign of a significant restenosis or reocclusion, and status was then confirmed by duplex ultrasound and angiography. At the end of the study period, all patients registered alive with a patent reconstruction were invited to an end of study examination with ankle-arm pressure measurement and ultrasound assessment. If symptoms had recurred

and ultrasound confirmed a  $\geq 50\%$  restenosis or reocclusion in the treated segment, the event was registered at the time of reoccurrence of symptoms. For patients declining the end of study follow up, data were censored at the previous follow up when the status of patency was known.

A duplex ultrasound examination of the distal abdominal aorta, the iliac and common femoral arteries was performed by two experienced ultrasound technicians. A velocity increase in the common iliac artery of  $>2.5$  compared to the velocity proximally to the aortic bifurcation associated with a loss of reverse flow component in the external iliac artery was the criterion for a  $\geq 50\%$  stenosis.<sup>30</sup> Patency was defined as freedom from either reocclusion or  $\geq 50\%$  restenosis, both of these criteria being used as end-points. Median follow-up time for all procedures was 22 months (range 0–55 months).

Blood for analysis of fasting plasma homocysteine (Hcy) (normal range 0–15  $\mu\text{mol/l}$ ), fibrinogen (Fibr) (normal range 2–4 g/l), D-dimer (D dim) (normal range 0.0–0.5 mg/l), activated protein C resistance, with exception of patients on oral anticoagulation (normal value  $<2$ ) was drawn upon admission.

Calculations of technical success rates are based on all procedures performed in the study period (included and excluded procedures). All remaining calculations and comparisons of patency rates were based on successfully treated cases.

Comparison of patency rates between groups with respect to age, sex, risk factors (Table 1), anatomy of the lesions and run-off, homocysteine and haemostatic risk factors, treatment with platelet inhibitors, cholesterol lowering medication, beta-blockers or calcium receptor antagonists, indication for treatment and the endovascular technique applied was performed with univariate analysis (log-rank test).

The values of homocysteine, fibrinogen and D-dimer were dichotomised by division into tertiles and quartiles for univariate and multivariate analysis. High versus low levels were compared in a sequential manner with respect to events (Table 2). Results with  $p$  values  $<0.2$  were included in a Cox multivariate analysis. For factors yielding more than one  $p$  value

$<0.2$  on log-rank test, only the percentile of the lowest  $p$  value was included in the multivariate analysis. All data were prospectively registered in a vascular registry run by the department and analysed with SPSS 11.0 for Windows. Statistical significance was accepted at  $p < 0.05$ .

## Results

The technical success rate for all procedures (included and excluded) was 93% (Fig. 1), 96% for stenting and 91% for PTA. The 30 days mortality after the procedures was nil. Procedure-related complications are listed in Table 3. Only three cases with critical ischaemia resulted in amputation. All three cases had severe distal disease preventing limb salvage and were amputated despite a patent iliac reconstruction.

The 1-year cumulative primary patency rate for all procedures (included and excluded) was 85% (Fig. 1). The 1-year primary patency rate was 89% for stenoses and 71% for occlusions. The 12 and 18 months patency rates after treatment with kissing stents were 68 and 61%, respectively.

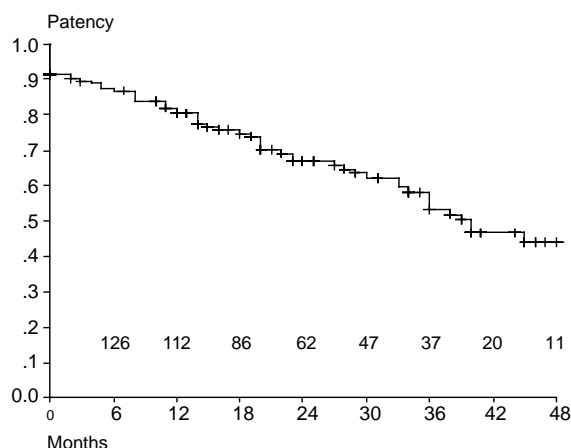
Univariate analysis showed significantly inferior patency rates in arteries treated for occlusions as compared to stenoses ( $p=0.009$ ) (Fig. 2). Patency was also significantly inferior after treatment with kissing stents ( $p=0.005$ ) (Fig. 3), for homocysteine values above the 75 percentile ( $>13.36 \mu\text{mol/l}$ ) ( $p=0.045$ ) (Fig. 4) and plasma fibrinogen values above the upper tertile ( $>3.5 \text{ g/l}$ ) ( $p=0.047$ ) (Fig. 5; Table 2).

On multivariate analysis, treatment for occlusions ( $p=0.005$ ), values of plasma homocysteine  $>13.36 \mu\text{mol/l}$  (highest quartile) ( $p=0.005$ ) and serum fibrinogen  $>3.5 \text{ g/l}$  (upper 66%) ( $p=0.047$ ) were independent predictors of failure (Table 4). D-dimer levels, Activated protein C resistance, clinical risk factors (Table 1), degree of ischaemia, length of the reconstruction, runoff, medical treatment and interventions with PTA only (without stent) were not significantly associated with failure.

**Table 2.** Percentiles of measured values of homocysteine, fibrinogen and D-dimer were used for division into groups for comparison with log-rank test in a stepwise manner with respect to patency

Study VI. Percentiles—log-rank test											
25	$p$	33	$p$	50	$p$	66	$p$	75	$p$	N.V.*	$p$
8.6	0.09	8.8	0.14	10	0.35	11.8	0.64	13.36	0.045	$\leq 15$	0.4
3.3	0.22	3.5	0.048	3.7	0.23	4.1	0.8	4.3	0.83	$\leq 4$	0.64
0.26	0.27	0.29	0.84	0.4	0.13	0.57	0.49	0.71	0.58	$\leq 0.5$	0.36

\* N.V. Normal value



**Fig. 1.** Patency rates of 197 common iliac endovascular interventions in 149 patients. Calculation is based on all cases treated in the study period (cases included as well as excluded from the study). Patency is defined as an open artery without  $\geq 50\%$  restenosis. The numbers under the curve display patients at risk.

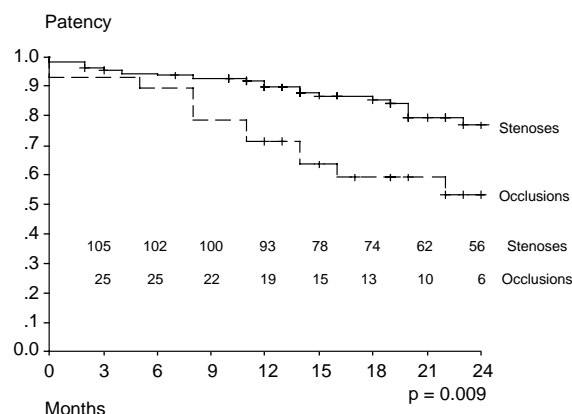
### Discussion

The technical success rate of 93% and 1-year primary patency rate of 89% after treatment of stenoses and 71% for occlusions in the present series are acceptable and comparable to those reported by others.<sup>1,2</sup> However, the 1-year patency rates after treatment with kissing stents in our series are lower than previously reported, probably due to the high number of occlusion treated with this technique.<sup>31</sup> The technical success rate was better in the stented group as compared to PTA alone. The risk of complications was not increased in the groups treated with additional stenting. Only one reocclusion demanded surgery (aorto-bifemoral bypass). All other cases suffering symptoms demanding reintervention were treated successfully with endovascular techniques.

The fact that the technical success was determined on the basis of completion angiography only and not duplex ultrasound may be regarded as a limit to the validity of the study, since residual stenoses may be difficult to detect on angiograms. However, the reliability of duplex ultrasound is also debateable for reasons of operator dependency and a sensitivity of 80% and specificity of 95% in detecting 50% stenosis.<sup>32</sup>

**Table 3. Procedure-related complications to 139 common iliac endovascular procedures in 103 patients**

Complication	n	Treatment	n
Distal embolisation	1	Aspiration	1
Dissection	5	Stent	5
Haematoma	4	Conservative	4
Bleeding	1	Operation	1
Perforation	1	Covered stent	1

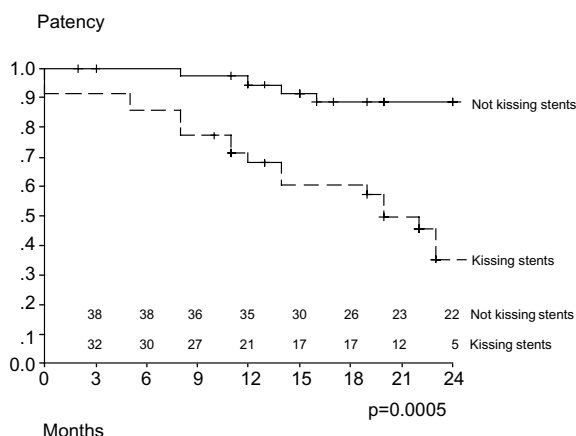


**Fig. 2.** Comparison of patency rates of 139 common iliac endovascular procedures in patients with occlusions (broken line) and stenoses (unbroken line). The numbers under the curve indicate patients at risk.

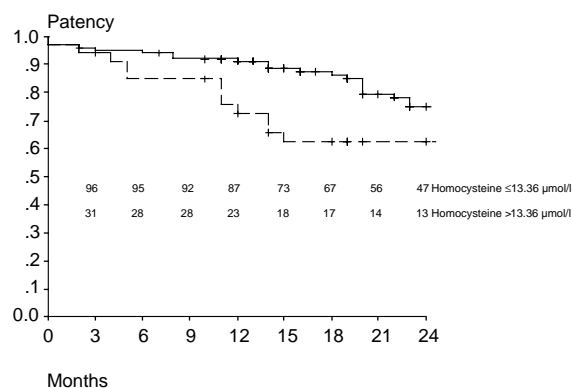
The patency rate following treatment of occlusions was significantly worse than after treatment of stenoses, which is consistent with earlier reports of endovascular treatment of iliac as well as superficial femoral arteries.<sup>1,2,9</sup> This may be due to an increased thrombogenicity secondary to a greater arterial trauma needed for a satisfactory result.

The relationship between elevated homocysteine and atherosclerosis was first observed by McCully in patients with homocysteinuria, a metabolic deficiency resulting from an autosomal recessive error.<sup>33</sup> Mild hyperhomocysteinemia can be caused by deficiency of vitamin B12, B6 and Folate, various life style factors as well as age,<sup>34</sup> and is a predictor of cardiovascular and all cause mortality in a dose dependent fashion.<sup>35</sup>

The results of observational studies on the relationship between failure after coronary bypass or

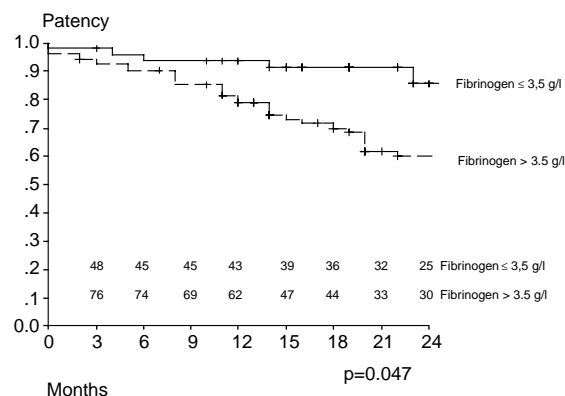


**Fig. 3.** Comparison of patency rates after endovascular treatment of symptomatic atherosclerotic lesions in common iliac arteries with stent: with kissing technique (broken line) and without kissing technique (unbroken line). The numbers under the curve indicate patients at risk.



**Fig. 4.** Comparison of homocysteine values with respect to patency rates after endovascular treatment of symptomatic occlusive disease in the common iliac arteries: The upper 25% ( $> 13.36 \mu\text{mol/l}$ ) (broken line) compared with the lower 75% ( $\leq 13.36 \mu\text{mol/l}$ ) (unbroken line) of measured values. The numbers displayed under the curve signify patients at risk.

interventions and homocysteine levels have so far been ambiguous.<sup>13,14</sup> The results of retrospective as well as prospective observational studies on peripheral vascular and endovascular surgery are no less conflicting. An association between hyperhomocysteinemia and failure was not proven in seven of the nine studies hitherto published.<sup>9,15–22</sup> Two of these studies are based on a case mix of treatment in different anatomical locations performed with a variety of techniques.<sup>18,22</sup> Three other studies are based on results after infrainguinal bypass surgery, either with



**Fig. 5.** Comparison of patency rates after 139 common iliac endovascular interventions in patients with fibrinogen  $> 3.5$  and  $\leq 3.5 \text{ g/l}$ . The numbers under the curve indicate patients at risk.

a mix of prosthetic bypass and vein or vein bypass above and below the knee.<sup>15–17</sup> Only four studies are prospective and of one treatment modality performed in a well defined arterial segment.<sup>9,19–21</sup>

In two earlier studies performed in our group, hyperhomocysteinemia was not a predictor of failure after endovascular treatment of the above-knee femoro-popliteal artery, and low homocysteine levels were predictors of restenosis after carotid endarterectomy.<sup>9,19</sup> In the latter study the numbers included were low and events few, rendering the probability of a type 1 error likely. In the present study, homocysteine levels in the upper quartile ( $> 13.36 \mu\text{mol/l}$ ) were independent predictive of failure. These conflicting results may be explained by anatomically determined differences in arterial susceptibility to homocysteine. This view is consistent with the findings of the Hoorn study of an association between hyperhomocysteinemia and risk for aortoiliac but not isolated crural occlusive disease<sup>36</sup> and the lack of association between the progression of carotid disease and elevated homocysteine in another study.<sup>12</sup> Furthermore, the mean follow-up time of our studies is relatively short, and thus we are likely detecting intimal hyperplasia not progressive atherosclerosis.

The increased risk of restenosis in patients with fibrinogen levels  $> 3.5 \text{ g/l}$  in the present study is consistent with a previous report, and may reflect an increased procoagulant or inflammatory activity in patients.<sup>37</sup> Assuming that increased procoagulant status plays a role in the pathogenesis of restenosis, pre- and post-procedural fibrinogen levels may be predictive of failure. The results of studies on the subject have so far been conflicting. In one study of 27 renal angioplasties, fibrinogen levels were significantly associated with failure,<sup>38</sup> but only two of four major studies on restenosis after coronary angioplasty found fibrinogen predictive of failure.<sup>39–42</sup> Reviewing studies on the association between fibrinogen levels and failure after peripheral arterial intervention the results appear to be no less conflicting. However, when grouping the studies according to the localisation of the treatment in the arterial tree, a clearer picture emerges: Of three prospective studies of endovascular intervention, based on a case mix (anatomical localisation not defined), failure had no association with fibrinogen levels in one, low levels were predictor of failure in

**Table 4.** Multivariate analysis (Cox' proportional hazard model) of risk factors demonstrated with univariate analysis to be significantly associated with patency rates in 139 iliac artery endovascular reconstructions

Variables	$\beta$	Standard error	p value	Hazard ratio	95% CI
Occlusion vs. stenosis	0.983	0.350	0.005	2.671	1.344–5.307
Hcy $> 13.36 \mu\text{mol/l}$	0.879	0.332	0.007	1.935	1.269–4.569
Fibrinogen $> 3.5 \text{ g/l}$	0.660	0.327	0.047	1.935	1.010–3.707



another and high levels in the third.<sup>43–45</sup> Four prospective studies on results after interventions in the femoro-popliteal segment demonstrate that fibrinogen levels are not predictive of failure.<sup>9,46–48</sup> Whereas two studies, the present included, on results of intervention in the iliac artery both find fibrinogen levels predictive of failure in this segment.<sup>10</sup>

The aforementioned studies support the view that there may be regional biological differences in the arterial tree that explain the variation in reaction to intervention as well as treatment results. This view is further supported by Schillinger *et al.*, who investigated the inflammatory response after endovascular stenting and found higher values of CRP and fibrinogen after treatment of the femoro-popliteal artery than the iliac artery.<sup>25</sup> Even if fibrinogen levels are not predictive of failure after femoro-popliteal PTA, they are associated with the severity of lower limb ischaemia, with higher values in patients with critical limb ischaemia ( $p < 0.05$ ).

The number of studies on the association between D-dimer levels and the risk of failure after endovascular intervention are scarce. One study of coronary endovascular intervention compared patients with myocardial infarction (MI) and patients with stable coronary disease (SCD). The MI patients had significantly higher D-dimer levels than the patients in the SCD group, the elevation of D-dimer being a significant predictor for restenoses in the MI group.<sup>49</sup> In a previous study we found that elevated pre-treatment level of D-dimer was a significant predictor of failure after endovascular treatment of the above-knee femoro-popliteal artery<sup>9</sup> but not after carotid endarterectomy.<sup>19</sup>

Our findings suggest an increased procoagulant activity, either primary or secondary to inflammation, is a predictor of endovascular treatment failure in the above-knee femoro-popliteal artery (D-dimer) and the common iliac artery (fibrinogen), but not after carotid surgery. The aetiology of restenoses and reocclusions after endovascular intervention in the common iliac artery is probably multifactorial. Factors enhancing the activity of the fibrinolytic system, the nature of the lesion treated and homocysteine levels above the upper range of normal are important risk factors for failure after endovascular treatment of the common iliac arteries.

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